

Indirect comparison of lixisenatide versus neutral protamine Hagedorn insulin as add-on to metformin and sulphonylurea in patients with type 2 diabetes mellitus

Lixisenatid versus NPH-Insulin als Therapieintensivierung nach Metformin und Sulfonylharnstoff bei Patienten mit Typ 2 Diabetes mellitus – Ergebnisse eines indirekten Vergleichs

Abstract

Objective: There is currently a lack of evidence from direct comparisons of treatment outcomes with lixisenatide versus neutral protamine Hagedorn (NPH)-insulin in type 2 diabetes mellitus (T2DM) patients with suboptimal glycaemic control with oral antidiabetic drugs (OADs). Hence, the current analysis indirectly compared available evidence on the risk of hypoglycaemia and weight change between lixisenatide and NPH-insulin based on randomized controlled trial (RCT) data with exenatide, insulin glargine and placebo as common references.

Methods: A systematic search of PubMed, Embase, the Cochrane database and clinical registries identified English- and German-language articles published from January 1980 to October 2012 reporting data from RCTs. Only publications of trials that reported outcomes from 24 to 30 weeks comparing glucagon-like peptide-1 receptor agonists or basal insulin versus another antidiabetic agent or placebo were included. Hypoglycaemia, patients at glycated haemoglobin (HbA_{1c}) target and discontinuations due to adverse events (AEs) were treated as binary variables, with risk ratios and odds ratios (ORs) calculated. HbA_{1c} and body weight were treated as continuous variables with difference in mean change from baseline (MD) calculated. Meta-analyses were performed with random effects models and indirect comparisons were performed according to Bucher's method.

Results: Seven RCTs (n=3,301 patients) comparing the efficacy and safety of lixisenatide, exenatide, insulin glargine and NPH-insulin with different antidiabetic treatments in adult patients with T2DM were included in the final analysis. In the adjusted indirect comparison, there was a significant difference in symptomatic hypoglycaemia (OR = 0.38; 95% CI = [0.17, 0.85]) and in confirmed hypoglycaemia (OR = 0.46; 95% CI = [0.22, 0.96]) favouring lixisenatide over NPH-insulin and comparable changes in HbA_{1c} from baseline (MD = 0.07%; 95% CI = [-0.26%, 0.41%]). In contrast to NPH-insulin, there was a significant reduction in body weight with lixisenatide (MD = -3.62 kg; 95% CI = [-5.86 kg, -1.38 kg]) at study completion. The number of discontinuations due to AEs numerically favoured NPH-insulin over lixisenatide (OR = 2.64; 95% CI = [0.25, 27.96]), with a broad confidence interval.

Conclusions: Lixisenatide treatment was associated with a lower risk of hypoglycaemia and a greater weight loss compared with NPH-insulin. Glycaemic control with lixisenatide treatment was comparable with NPH-insulin. These data suggest that lixisenatide is a beneficial treatment option for T2DM patients with inadequate glycaemic control on OADs, and is associated with reduced risk of hypoglycaemia and weight gain.

Keywords: lixisenatide, basal insulin, hypoglycaemia, weight change, type 2 diabetes, adjusted indirect comparison

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Zusammenfassung

Zielsetzung: Derzeit mangelt es an direkten Vergleichen von Behandlungsergebnissen zwischen Lixisenatid und NPH-Insulin bei Typ-2-Diabetikern (T2DM) mit suboptimaler Blutzuckerkontrolle unter einer oralen Kombinationstherapie aus Metformin und einem Sulfonylharnstoff. Deshalb untersucht der vorliegende adjustierte indirekte Vergleich die verfügbare Evidenz primär zum Hypoglykämierisiko sowie zur Gewichtsveränderung zwischen Lixisenatid und NPH-Insulin auf Basis randomisierter kontrollierter Studien mit den Brückenkomparatoren Exenatide, Insulin glargin und Plazebo.

Methoden: Zwei systematische Literaturrecherchen in PubMed, Embase, der Cochrane-Datenbank sowie in klinischen Registern identifizierten englisch- und deutschsprachige Publikationen, die entsprechende Ergebnisdaten aus randomisierten klinischen Studien (RCTs) enthielten und die zwischen Januar 1980 und Oktober 2012 veröffentlicht worden waren. Bestimmt durch die GetGoal-S Studie (Lixisenatid) mit einer Analyse der primären Endpunkte nach 24 Wochen, wurden nur Publikationen eingeschlossen, die Ergebnisse aus 24–30-wöchigen Studien zum Vergleich von GLP-1 Rezeptoragonisten oder Basalinsulinen vs. andere Antidiabetika oder Plazebo umfassten. Für die binären Ergebnisvariablen Hypoglykämiehäufigkeit, Anteil der Patienten mit dem erreichten HbA_{1c}-Zielwert sowie Studienabbrüche wegen unerwünschter Ereignisse wurden die relativen Risiken (RR) sowie die Odds Ratios (OR) als statistische Maße verwendet. Für die kontinuierlichen Ergebnisvariablen glykosyliertes Hämoglobin (HbA_{1c}) und Körpergewicht wurden die Differenzen der mittleren Veränderungen zum Ausgangswert (MD) als statistisches Maß verwendet. Notwendige Metaanalysen wurden auf Basis von Modellen mit zufälligen Effekten durchgeführt, die indirekten Vergleiche nach der Methode von Bucher.

Ergebnisse: Sieben RCTs (n=3.301 Patienten), die die Wirksamkeit und Sicherheit von Lixisenatid, Exenatide, Insulin glargin oder NPH-Insulin gegen unterschiedliche Komparatoren bei erwachsenen Patienten mit T2DM verglichen, wurden in die abschließende Analyse einbezogen. Im adjustierten indirekten Vergleich zeigte sich ein signifikanter Unterschied in Bezug auf die Häufigkeit symptomatischer Hypoglykämien (OR = 0,38; 95% KI = [0,17; 0,85]) sowie hinsichtlich des Auftretens von bestätigten Hypoglykämien zugunsten von Lixisenatid (OR = 0,46; 95% KI = [0,22; 0,96]) bei vergleichbarer HbA_{1c}-Senkung gegenüber dem Ausgangswert (MD = 0,07%; 95% KI = [-0,26%; 0,41%]). Unter Lixisenatid zeigte sich im Gegensatz zu NPH-Insulin auch eine signifikante Abnahme des Körpergewichts zum Studienende (MD = -3,62 kg; 95% KI = [-5,86kg; -1,38kg]). Die Zahl der Therapieabbrüche aufgrund von unerwünschten Ereignissen war unter NPH-Insulin numerisch geringer als unter Lixisenatid (OR = 2,64; 95% KI = [0,25; 27,96]), aber mit einem sehr breiten Konfidenzintervall.

Schlussfolgerung: Die Therapieintensivierung mit Lixisenatid ging mit einem niedrigeren Hypoglykämierisiko sowie einer deutlichen Gewichtsabnahme gegenüber NPH-Insulin einher. Die glykämische Kontrolle war unter beiden Therapieregimen vergleichbar. Somit stellt Lixisenatid gegenüber NPH-Insulin eine geeignete Behandlungsalternative für T2DM-Patienten mit unzureichender Blutzuckerkontrolle dar, bei denen der behandelnde Arzt ein erhöhtes Hypoglykämierisiko sowie eine Gewichtszunahme ausschließen möchte.

Schlüsselwörter: Lixisenatid, Basalinsulin, Hypoglykämie, Gewichtsveränderung, Typ 2 Diabetes, adjustierter indirekter Vergleich

Introduction

Glycaemic management, in addition to diet, exercise and education, remains the foundation of type 2 diabetes mellitus (T2DM) treatment programmes. There are a number of pharmacological agents available for glycaemic management in T2DM, with patients usually initiated on oral antidiabetic drugs (OADs) either as monotherapy or in combination. However, when OADs provide suboptimal glycaemic control, patients may require treatment with basal insulin to prevent long-term microvascular and macrovascular complications related to poor metabolic control [1].

The goal of insulin therapy is to deliver effective glycaemic control without hypoglycaemia or unacceptable weight gain [2], both of which have a substantial clinical impact on quality of life, morbidity and mortality [3]. In addition to a greater potential for adverse cardiovascular events, weight increase can cause insulin resistance in clinically obese patients. Because weight increase ensues shortly after the initiation of treatment with insulin, it may interfere with patients' adjustment to insulin therapy and may undermine appropriate diabetes self-management behaviours [4].

In contrast to human basal insulin (neutral protamine Hagedorn, NPH), basal insulin analogues (glargine, detemir) provide relatively uniform insulin levels throughout the day and night. Of the available insulin formulations, insulin glargine and insulin detemir are associated with less nocturnal hypoglycaemia than NPH-insulin [4], [5]. Insulin detemir is associated with less weight gain than NPH-insulin [4]. For insulin glargine and NPH-insulin, different effects on weight gain have been reported in patients with T2DM. In some randomized controlled trials (RCTs), less weight gain was evident with insulin glargine [6], whereas other studies found similar weight gain with glargine and NPH-insulin [7]. Drugs targeting the incretin system, such as the oral dipeptidyl peptidase-4 (DPP-4) inhibitors and the injectable glucagon-like peptide-1 (GLP-1) receptor agonists, have shown improvements in glycaemic values when added to metformin in patients with T2DM [8]. GLP-1 receptor agonists are associated with a higher reduction in glycated haemoglobin (HbA_{1c}) values than DPP-4 inhibitors. Moreover, GLP-1 receptor agonists have a beneficial effect on body weight, whereas DPP-4 inhibitors are weight-neutral [8].

For patients with inadequate glycaemic control with OAD combinations, treatment options in Germany include the addition of DPP-4 inhibitors, GLP-1 receptor agonists or basal insulin to current therapy [9]. Lixisenatide is a once-daily prandial GLP-1 receptor agonist for the treatment of adults with T2DM that has been shown to delay gastric emptying, enhance insulin secretion and inhibit glucagon release in patients with T2DM, with a beneficial effect on body weight and a low risk of hypoglycaemia. There is currently a paucity of evidence directly comparing the efficacy and safety of lixisenatide with that of NPH-insulin. Therefore, the objective of the current analysis was to

conduct a multi-step indirect comparison of evidence primarily on hypoglycaemia and weight change based on RCTs that enrolled patients with prior suboptimal glycaemic control with OADs (metformin and sulphonylurea) who received treatment intensification with lixisenatide or NPH-insulin.

Methods

Systematic literature review

Two systematic reviews of the literature were performed in separate but overlapping processes that followed similar protocols. The first review evaluated available published data on the clinical efficacy and safety of GLP-1 receptor agonists and OADs. The second review evaluated published data on the clinical efficacy and safety of basal insulin therapies. In order to identify English- and German-language clinical articles published from January 1980 to October 2012 and reporting data from RCTs, the following databases were searched: MEDLINE (PubMed); ELSEVIER (Embase); the Cochrane Collaboration Central Register of Clinical Trials (CENTRAL); and clinical registries. The search criteria included articles published from 1980 onwards because, prior to that date, data from RCTs were not systematically analyzed using the intent-to-treat population, thus limiting the interpretation and comparability of the results.

Article selection

The criteria for article selection are summarized and the article selection algorithm is shown in Attachment 1 and Attachment 2, respectively (the full syntax is available upon request to the authors). The search for trials of OAD and insulin therapies identified 6,820 abstracts (4,502 from the OAD systematic review and 2,318 from the insulin systematic review). Further to the papers identified in the systematic reviews, an additional 429 abstracts (213 from the OAD systematic review and 216 from the insulin systematic review) were identified from a search of meeting abstracts from annual conferences of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD), and by screening the reference lists of relevant literature reviews, systematic reviews and meta-analyses. After the removal of duplicate references and abstract screening, 1,160 publications were retrieved for full-text screening. During full-text screening, 438 publications did not meet the inclusion criteria. The most common reasons for exclusion were trials without a treatment of interest; monotherapy trials shorter than 12 weeks; oral combination therapy trials shorter than 24 weeks; and trials that did not report predefined outcomes for the analysis (Attachment 2). After screening for primary publications, time points for reported outcomes, OAD exposure and patient populations who were not receiving insulin, 104 publications remained. Of these, six were eligible for inclusion in the

final quantitative analysis based on additional exclusion criteria (Attachment 2).

Analysis of these six publications was based on the development of an evidence network using pairwise comparisons. The network framework was composed of trials that assessed the efficacy and safety of add-on treatment with lixisenatide, exenatide, insulin glargine or NPH-insulin to basic therapy with metformin plus sulphonylurea. The final goal of the successive pairwise steps was to compare the efficacy and safety of lixisenatide versus NPH-insulin as add-on treatment to metformin plus sulphonylurea (Figure 1). From the study by Apovian et al. [10], only the subgroup of patients with a background diabetes treatment of metformin plus sulphonylurea was used.

Quantitative analyses: Selection criteria

The inclusion criteria for the quantitative analyses were: (i) comparisons of GLP-1 receptor agonists or basal insulin with either placebo or another class of antidiabetic agents; (ii) RCTs reporting outcomes between 24 and 30 weeks; and (iii) patients with T2DM who were unable to achieve adequate glycaemic control with combination OAD therapy. Trials were excluded if: (i) the same antidiabetic agent was evaluated; (ii) patients were not naïve to insulin treatment; and (iii) the use of background OAD therapy was stopped. Quality assessment on the studies selected for the quantitative analyses was conducted using the CONSolidated Standards Of Reporting Trials (CONSORT) checklist [11].

Data handling

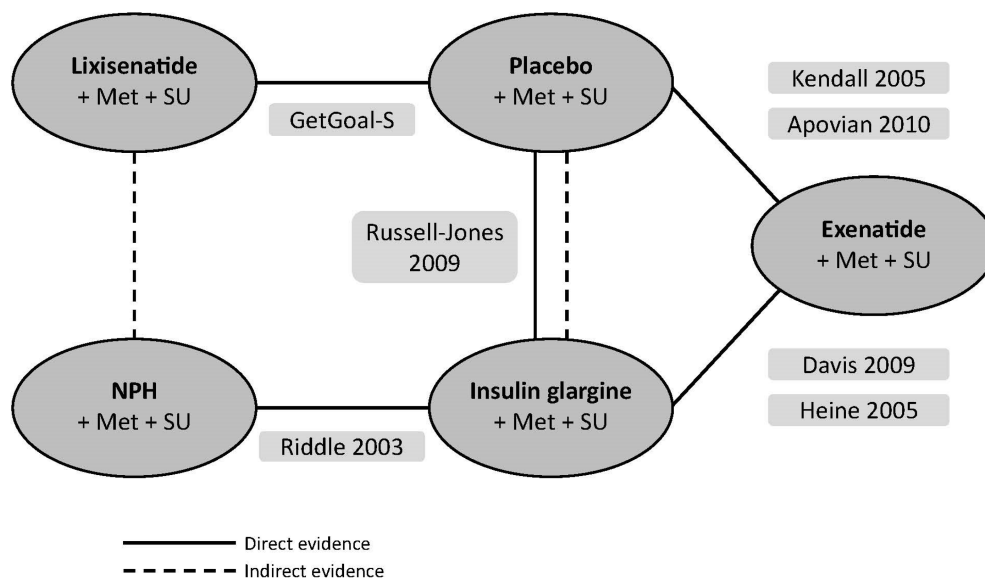
Data reported for confirmed hypoglycaemic episodes could contain symptomatic and non-symptomatic hypoglycaemia, but were subsequently confirmed by a low blood glucose or plasma glucose value. Data reported for overall hypoglycaemic episodes could contain confirmed and non-confirmed hypoglycaemia. Mean changes in HbA_{1c} and baseline body weight, including standard errors (SEs), were taken from the clinical study report (Sanofi, data on file) and not from the primary paper by Riddle et al. [12], as these values were not available in the published manuscript. In the article by Apovian et al. [10], the SEs for mean change in HbA_{1c} were ‘extracted’ from the graphs. Wherever possible, missing standard deviations (SDs) or SEs were requested from the corresponding author. In the Heine et al. study [13], the SEs of mean changes in both HbA_{1c} and body weight were not available and were thus obtained from values reported in the study by Davies et al. [14], which compared the same arms, when the first meta-analysis combining the two studies was performed. In order to validate this choice, data from the Heine paper were used to derive an SE on the difference between groups in the change in HbA_{1c} and body weight from baseline. This was then compared with the value obtained from the meta-analysis of Heine and Davis, to check their consistency. Although the studies differ with respect to the weight distribution, the results

were similar with respect to the estimated SE, which were then considered as supporting the a priori convention adoption. A control of consistency of the estimation with the SE of the difference between groups in the change from baseline for HbA_{1c} was done. When missing, SDs were derived from available SEs using the following formula: $SD = SE \times \sqrt{N}$, where N = number of patients. Missing patient numbers for each outcome (n) were computed from the percentages and denominators, for binary outcomes.

Statistical methods and software

An indirect comparison of NPH-insulin and lixisenatide was performed as recommended in the literature [15], [16]. The successive steps that were followed to build a final adjusted indirect comparison between lixisenatide and NPH-insulin are summarized in Figure 1. Briefly, Step 1 combined the studies by Kendall et al. [17] and Apovian et al. [10], comparing placebo versus exenatide in the first meta-analysis. Step 2 combined the studies by Davies et al. [14] and Heine et al. [13], comparing exenatide versus insulin glargine in the second meta-analysis. The first and second meta-analyses provided an indirect comparison between insulin glargine and placebo using exenatide as a common reference (Indirect Comparison 1). The result of Indirect Comparison 1 was combined with the study by Russell-Jones et al. [18], comparing insulin glargine versus placebo in the third meta-analysis. The third meta-analysis compared insulin glargine with placebo, and the results were used alongside those from the study by Riddle et al. [12], which compared insulin glargine with NPH-insulin, to perform Indirect Comparison 2, with insulin glargine as the common reference. The final indirect comparison (Indirect Comparison 3) between NPH-insulin and lixisenatide was conducted between Indirect Comparison 2 comparing NPH-insulin versus placebo and the GetGoal-S study (NCT00713830) comparing lixisenatide versus placebo, with placebo as the common reference (Figure 1).

Bucher’s pairwise indirect comparisons [15] were conducted with Microsoft Excel, and R software was used to perform meta-analyses to combine each set of trials that contributed to the pairwise comparisons. Statistics were directly computed into Excel to combine the data for the meta-analyses on relative measures (mean difference [MD], risk ratios [RR] or odds ratios [OR]) issued from adjusted indirect comparisons. An inverse variance weighting method was applied and weighted averages were computed to combine the data from the different studies in the meta-analysis [19]. As heterogeneity tests were sometimes statistically significant, exclusively random effects results were systematically used as inputs for indirect comparisons. Nevertheless, in the case of formal heterogeneity of effects, it was decided case-by-case whether the results of the meta-analyses could be used in further steps – for example, the results were used in cases of clear effects in the same direction. HbA_{1c} and body weight were treated as continuous outcomes and



- 1 = First meta-analysis: Placebo versus exenatide [10, 17]
 2 = Second meta-analysis: Insulin glargine versus exenatide [13, 14]
 3 = First indirect comparison: Insulin glargine versus placebo (via exenatide as reference)
 4 = Third meta-analysis: Insulin glargine versus placebo (direct comparison: Russell-Jones, 2009 [18] and Indirect Comparison 1)
 5 = Indirect Comparison 2: NPH versus placebo (via insulin glargine as reference and using Riddle [direct comparison NPH versus glargine] and third meta-analysis [placebo versus glargine])
 6 = Indirect Comparison 3 (lixisenatide versus NPH via placebo as reference using second indirect comparison [NPH vs. placebo] and GetGoal-S [lixisenatide versus placebo])
 Met = metformin; SU = sulphonylurea; NPH = neutral protamine Hagedorn; I = insulin

Figure 1: Evidence network

MDs were evaluated. Hypoglycaemia, patients at HbA_{1c} target and discontinuations due to AEs were treated as binomial outcomes, and RRs – as well as ORs – were calculated. ORs are the common statistical measure for binary data, but RRs are better for interpretation. For each binary endpoint and each analysis, estimates of the relative measure between lixisenatide and NPH-insulin were reported, with 95% two-sided confidence intervals (CIs). Mean changes in HbA_{1c} were re-analyzed with the same network as a sensitivity analysis, omitting the trial by Apovian et al. [10] because it included fewer patients than the other studies. The SAS GLIMMIX procedure for random-effects mixed treatment comparison was used to model binomial data for sensitivity analyses.

Results

Studies and patient characteristics

Seven RCTs were included in the final analysis. The literature search identified six RCTs that met the trial selection criteria (Attachment 2), and were used for the pairwise analysis. The GetGoal-S trial [20] was added to include one study presenting evidence on lixisenatide compared with placebo (Figure 1).

The seven RCTs (n=3,301 patients) compared the efficacy and safety of: lixisenatide versus placebo; exenatide versus placebo or insulin glargine; and insulin glargine versus placebo or NPH-insulin in adult patients with T2DM requiring a second- or third-line treatment agent owing to inadequate glycaemic control (Table 1). Patients in all studies continued taking metformin plus sulphonylurea when exenatide, lixisenatide or insulin therapy was initiated.

Baseline demographic characteristics per treatment groups are summarized by study in Table 1. Mean age (range 55.0–59.8 years), mean HbA_{1c} (range 7.9–8.7%) and mean body mass index (BMI; 30.1–34.6 kg/m²) were similar across studies. The proportion of female patients was 29.7–69.0%; mean disease duration was 7.6–9.9 years and mean weight was 82.3–101.4 kg.

Hypoglycaemia, weight changes and HbA_{1c}

The incidence of hypoglycaemia and weight change is summarized by study in Table 2. The proportion of patients with confirmed hypoglycaemia (definitions by plasma glucose or blood glucose values differ slightly between studies [<60 to <55 mg/dL; <3.4 to <3.1 mmol/L]) was higher with lixisenatide, exenatide and in-

Table 1: Baseline characteristics from the seven trials included for indirect comparison

Study	Ratner, 2011 [20] (GetGoal-S)	Apovian, 2010 [10]*	Kendall, 2005 [17]	Heine, 2005 [13]	Davies, 2009 [14]	Russell-Jones, 2009 [18]	Riddle, 2003 [12]
Study design	Double-blind, multicentre RCT	Double-blind, multicentre RCT	Double-blind, multicentre RCT	Open-label, multicentre RCT	Open-label, multicentre RCT	Open-label, multicentre RCT	Open-label, multicentre RCT
Population	T2DM poorly controlled with metformin	T2DM poorly controlled with OADs	T2DM poorly controlled with OADs	Insulin-naïve T2DM poorly controlled with OADs	T2DM poorly controlled with OADs	Insulin-naïve T2DM poorly controlled with OADs	Insulin-naïve T2DM poorly controlled with OADs
Sample size, n	859	69	488	549	234	346	756
Study duration	24 weeks	24 weeks	30 weeks	26 weeks	26 weeks	26 weeks	24 weeks
Treatment groups	Lixi (n=574) Placebo (n=285)	Exenatide (n=33)* Placebo (n=36)*	Exenatide (n=241) Placebo (n=247)	Exenatide (n=282) Insulin glargine (n=267)	Exenatide (n=118) Insulin glargine (n=116)	Insulin glargine (n=232) Placebo (n=114)	Insulin glargine (n=367) NPH (n=389)
Mean age, years (SD)	57.0 (9.8)	55.9 (9.3)	55.0 (10)	59.8 (8.8)	56.8 (10.2)	57.5 (10.5)	55 (9.5)
Female, %	50.5	52	40.7	45.0	29.7	40	55
Disease duration, years (SD)	9.1 (6.0)	8.5 (7.5)	8.7 (6.4)	9.9 (6.0)	9.0 (4.6)	9.7 (6.4)	8.4 (5.6)
Mean HbA_{1c}, % (SD)	8.3 (0.9)	8.0 (0.8)	8.5 (1.1)	8.2 (1.0)	8.7 (0.68)	8.2 (0.9)	8.6 (0.9)
Mean weight, kg (SD)	82.3 (21.8)	98.6 (20.1)	98 (21.0)	87.5 (16.9)	101.4 (19.8)	85.0 (17.9)	95.4 (17.7)
BMI, kg/m² (SD)	30.1 (6.6)	34.0 (3.7)	34.0 (6.0)	31.4 (4.4)	34.6 (5.7)	30.3 (5.3)	32.5 (4.6)

*Only a subgroup of patients receiving Met + SU (n=69/194) as basal therapy was used for this indirect comparison.
 RCT = randomized, controlled trial; T2DM = type 2 diabetes mellitus; OAD = oral antidiabetic drug; Lixi = lixisenatide; NPH = neutral protamine Hagedorn; SD = standard deviation;
 HbA_{1c} = glycated haemoglobin; NR = not reported; BMI = body mass index; Met = metformin; SU = sulphonylurea.

sulin glargine compared with placebo, but similar between exenatide and insulin glargine. The incidence of confirmed hypoglycaemia was higher with NPH-insulin compared with insulin glargine (Table 2). Similar results were obtained for overall hypoglycaemia (Table 2).

Weight changes were greater with lixisenatide (decrease), exenatide (decrease) and insulin glargine (increase) compared with placebo, as well as with exenatide (decrease) compared with insulin glargine (increase). Weight changes with insulin glargine (increase) and NPH-insulin (increase) were similar (Table 2).

Changes in HbA_{1c} are summarized in Table 3. Baseline HbA_{1c} parameters were similar across studies. Greater changes in HbA_{1c} values were observed with lixisenatide, exenatide and insulin glargine compared with placebo. Similar changes in HbA_{1c} parameters were observed with exenatide compared with insulin glargine and with insulin glargine compared with NPH-insulin (Table 3).

Treatment-emergent adverse events

The numbers of discontinuations due to treatment-emergent adverse events (TEAEs) were small in the various treatment arms of the studies (minimum 0.7%, maximum 9.6%) and no clear trends across compared treatments could be seen – for example, exenatide versus placebo: 4.2% versus 5.1% [10] and 9.1% versus 4.5% [17] (Table 3).

Results of indirect comparisons

Hypoglycaemia

There were significantly fewer patients who experienced hypoglycaemia receiving lixisenatide compared with NPH-insulin (OR: 0.38; 95% CI: 0.17, 0.85; RR: 0.56; 95% CI: 0.32, 0.96), with an implied risk reduction of 44%. Moreover, lixisenatide showed a trend towards better results compared with NPH-insulin with respect to confirmed hypoglycaemia (OR: 0.46; 95% CI: 0.22, 0.96; RR: 0.61; 95% CI: 0.33, 1.09), or a risk reduction of 39% (Table 4). A forest plot of the results of the indirect comparison with respect to hypoglycaemia is shown in Figure 2.

Weight change

Differences in body weight at study completion favoured lixisenatide over NPH-insulin, with lixisenatide patients experiencing significantly greater weight loss compared with NPH-insulin patients (MD: -3.62 kg; 95% CI: -5.86, -1.36 kg) (Table 4). There was a formal heterogeneity ($p=0.002$) of effects for the Davies and Heine studies, both comparing insulin glargine with exenatide, but the effects were clearly in the same direction (MDs: 5.7 kg vs. 4.1 kg).

Table 2: The incidence of hypoglycaemia and weight changes by study

Study	Treatment	Patients with confirmed hypoglycaemia*, n (%)	Patients with overall hypoglycaemia*, n (%)	Mean change in weight, kg (SD)
Ratner, 2011 [20] (Get Goal-S)	Lixi (n=574)	70 (12.2)	88 (15.3)	-1.8 (4.5)
	Placebo (n=285)	24 (8.4)	35 (12.3)	-0.9 (3.3)
Apovian, 2010 [10]	Exenatide (n=33)	NA	NA	-5.2 (9.2)
	Placebo (n=36)	NA	NA	-3.6 (9.6)
Kendall, 2005 [17]	Exenatide (n=241)	67 (27.8)	67 (27.8)	-1.6 (3.1)
	Placebo (n=247)	31 (12.6)	31 (12.6)	-0.9 (3.1)
Heine, 2005 [13]	Exenatide (n=282)	NA	NA	-2.3
	Insulin glargine (n=267)	NA	NA	1.8
Davies, 2009 [14]	Exenatide (n=118)	37 (31.4)	59 (50.0)	-2.7 (3.1)
	Insulin glargine (n=116)	42 (36.2)	68 (58.6)	3.0 (3.2)
Russell-Jones, 2009 [18]	Insulin glargine (n=232)	67 (28.9)	67 (28.9)	1.6 (5.0)
	Placebo (n=114)	19 (16.7)	19 (16.7)	-0.4 (4.2)
Riddle, 2003 [12]	Insulin glargine (n=367)	168 (45.8)	282 (76.8)	3.0 (3.8)
	NPH (n=389)	206 (53.0)	315 (81.0)	2.8 (3.9)

*Definitions of confirmed hypoglycaemia differ slightly between studies: Plasma glucose or blood glucose value <60–<55 mg/dL (<3.4–<3.1 mmol/L). Lixi = lixisenatide; NPH = neutral protamine Hagedorn; NA = data not available; SD = standard deviation.

Table 3: Glycated haemoglobin parameters and incidence of discontinuations due to treatment-emergent adverse events (TEAEs) by study

Study	Ratner, 2011 [20] (GetGoal-S)	Apovian, 2010 [10]	Kendall, 2005 [17]	Heine, 2005 [13]	Davies, 2009 [14]	Russell-Jones, 2009 [18]	Riddle, 2003 [12]
Treatment	Lixisenatide (n=544)	Exenatide (n=33)	Exenatide (n=230)	Exenatide (n=275)	Exenatide (n=96)	Insulin glargine (n=232)	Insulin glargine (n=367)
	Placebo (n=274)	Placebo (n=36)	Placebo (n=238)	Insulin glargine (n=260)	Insulin glargine (n=102)	Placebo (n=114)	NPH (n=389)
Mean baseline HbA _{1c} (SE)	8.3 (0.9)	8.0 (0.8)	8.5 (1.0)	8.2 (1.0)	8.7 (0.7)	8.2 (0.9)	8.6 (0.9)
Mean change (SD)	-0.9 (1.4)	-1.4 (1.2)	-0.8 (1.2)	-1.1	-1.3 (0.9)	-1.1 (1.4)	-1.7 (0.8)
Patients at HbA _{1c} target (<7%), n (%)	198 (36.4)	-	70 (30.0)	127 (46.0)	-	-	213 (58.0)
Discontinuations due to TEAEs, n (%)	48 (8.4)	4 (4.2)	22 (9.1)	27 (9.6)	7 (5.9)	5 (2.2)	7 (1.9)

NPH = neutral protamine Hagedorn; HbA_{1c} = glycated haemoglobin; SE = standard error; SD = standard deviation.

Glycated haemoglobin

The successive steps in the indirect comparison analysis (Attachment 4) led to a final comparison of lixisenatide versus NPH-insulin showing comparable results for HbA_{1c} changes from baseline, with or without inclusion of the Apovian et al. study data [10] (MD: 0.07%; 95% CI: -0.26%, 0.41% [with [13]] and MD: 0.17%; 95% CI: -0.12, 0.46 [without [10]]), as well as for HbA_{1c} at target (OR: 0.58; 95% CI: 0.25, 1.32; RR: 0.58; 95% CI: 0.31, 1.10) (Table 4). There was a trend for formal heterogeneity (p=0.1) of effects for the Kendall [17] and Apovian [10] studies, both comparing placebo with exenatide, but the effects were clearly in the same direction (MDs: 1.0% vs. 0.5% kg).

Discontinuations due to AEs

Discontinuations due to AEs numerically favoured NPH-insulin over lixisenatide in the point estimates of OR and RR (OR: 2.64; 95% CI: 0.25, 27.96; RR: 2.52; 95% CI: 0.25, 25.02) (Table 4). Due to the small number of discontinuations due to AEs in the various treatment arms of the studies, some heterogeneity in the combined study results for comparison of exenatide versus placebo [10], [17], and some inconsistency between direct and indirect results of the comparison of insulin glargine versus placebo, the results seem inconclusive. This was reflected by the broad confidence intervals for both OR and RR estimates.

Sensitivity analyses

Sensitivity analyses were performed excluding studies investigating exenatide or calculating the indirect comparison via insulin glargine as a reference, and are shown in Attachment 3. Conclusions from the analysis performed without the exenatide loop were similar to those in the analysis presented here; only the premature discontinuation due to AE was less robust. Stepwise comparisons performed as part of the indirect comparison are shown in Attachment 4.

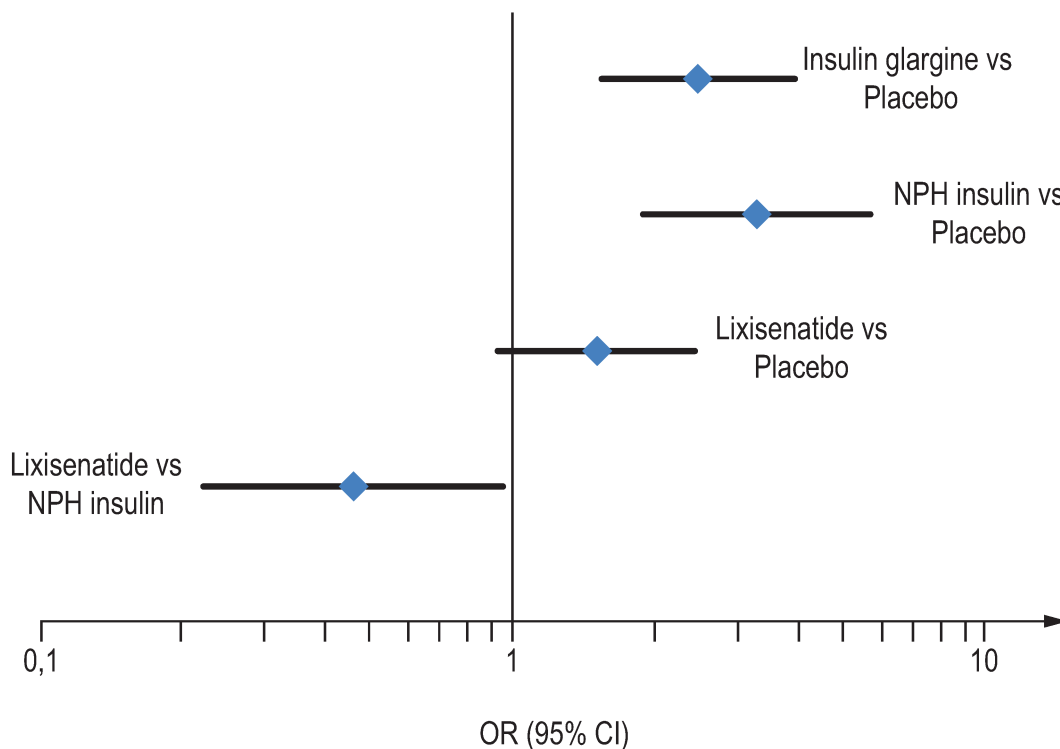
Discussion

The current analysis conducted an indirect comparison of the efficacy and safety of lixisenatide versus NPH-insulin as therapy intensification in the treatment of T2DM patients with prior suboptimal glycaemic control with OADs (metformin and sulphonylurea). This analysis showed that treatment with the GLP-1 receptor agonist lixisenatide was accompanied by significantly less overall hypoglycaemia and a trend to less confirmed hypoglycaemia. Moreover, differences in body weight at study completion favoured lixisenatide over NPH-insulin at comparable HbA_{1c} levels. Discontinuations due to AEs numerically favoured NPH-insulin, but this result was not conclusive due to small numbers of discontinuations due

Table 4: Summary results for all indirect comparisons following successive steps to build the final comparison of lixisenatide versus insulin neutral protamine Hagedorn in the treatment of type 2 diabetes mellitus

	Point estimate		95% CI
HbA_{1c} change from baseline	MD	0.07	-0.26; 0.41
HbA_{1c} change from baseline (without Apovian et al.)	MD	0.17	-0.12; 0.46
HbA_{1c} at target	OR	0.58	0.25; 1.32
HbA_{1c} at target	RR	0.58	0.31; 1.10
HbA_{1c} at target	RR-MTC	0.58	0.31; 1.10
Body weight, kg	MD	-3.62	-5.86; -1.38
Hypoglycaemia	OR	0.38	0.17; 0.85
Hypoglycaemia	RR	0.56	0.32; 0.96
Hypoglycaemia	RR-MTC	0.57	0.29.; 1.10
Confirmed hypoglycaemia	OR	0.46	0.22; 0.96
Confirmed hypoglycaemia	RR	0.61	0.33; 1.11
Confirmed hypoglycaemia	RR-MTC	0.61	0.32; 1.17
Discontinuation due to AEs	OR	2.64	0.25; 27.96
Discontinuation due to AEs	RR	2.52	0.25; 25.02
Discontinuation due to AEs	RR-MTC	3.33	0.12; 94.87

CI = confidence interval; HbA_{1c} = glycated haemoglobin; MD = mean difference; OR = odds ratio; RR = relative risk; MTC = mixed treatment comparison; AE = adverse event.



OR = odds ratio; CI = confidence interval; NPH = neutral protamine Hagedorn

Figure 2: Results of the adjusted indirect comparison with respect to the endpoint: Odds ratios (95%) of confirmed symptomatic hypoglycaemia

to AEs and heterogeneity in meta-analyses of studies, as well as in direct and indirect comparisons, resulting in broad confidence intervals for ORs and RRs.

Indirect comparisons of evidence are increasingly common in the scientific literature for T2DM when there is a paucity of head-to-head trials directly comparing treatment options [21], [22]. The results reported in the current analysis are consistent with those reported in an indirect analysis that compared the effect of antidiabetic agents added to metformin on glycaemic control, hypoglycaemia and weight change in patients with T2DM [21]. The latter analysis showed that biphasic insulin, GLP-1 receptor agonists and basal insulin were ranked highest for decreasing HbA_{1c}. However, GLP-1 receptor agonists did not increase the risk of hypoglycaemia and significantly decreased body weight, both of which increased with biphasic insulin and basal insulin [22].

The lower frequency of hypoglycaemia with comparable improvements in glycaemic control that were achieved with GLP-1 receptor agonists versus different types of insulin, as reported here, are important given the serious consequences of hypoglycaemic events. Symptomatic severe hypoglycaemia is associated with higher mortality in intensive as well as standard arms of RCTs [23], and severe hypoglycaemia is also associated with acute and chronic impairment of brain function [24]. Loss of consciousness poses a serious danger for patients as it increases fear and anxiety, whereas hypoglycaemic episodes increase the risk of dementia, which severely limits the individual's functional ability and has a considerable negative impact on the quality of life of patients with T2DM [25], as well as on healthcare costs [26].

In the current analysis, glycaemic control was comparable between lixisenatide and NPH-insulin. The availability of different treatments for T2DM that can confer glycaemic control provides clinicians with a broader range of options when developing individualized treatment regimens. However, other factors also need to be considered. Weight reduction through diet alone or with adjunctive medical or surgical intervention improves both glycaemic control and other cardiovascular risk factors. Indeed, even a modest weight reduction (5–10%) contributes meaningfully to achieving improved glucose control [1]. In a recent meta-analysis of randomized controlled trials [27], therapy with GLP-1 receptor agonists (exenatide given twice daily, exenatide given once weekly as a long-acting release, and liraglutide given once daily) resulted in a significantly greater weight loss compared with control groups (with different antidiabetic medication) of –2.8 kg (95% CI –3.4 to –2.3 kg). The greatest difference in weight change was seen for trials with control groups receiving insulin (–4.8 kg, –5.1 to –4.5 kg; six trials), OADs including metformin or sulphonylurea compounds (–3.0 kg, –4.9 to –1.2 kg; three trials) and dipeptidyl peptidase 4 inhibitors (–2.0 kg, –2.9 to –1.1 kg; two trials). Consistent with published evidence for GLP-1 receptor agonists, the current indirect comparison showed that lixisenatide treatment has a favourable weight reduction profile compared with NPH-insulin.

Weight reduction is one of the treatment targets in obese patients with T2DM. At least 5–7% weight loss is thought to reduce the risk of development of T2DM as a cardiovascular risk equivalent [28]. However, all insulin therapies are associated with some weight gain and some risk of hypoglycaemia. Although larger insulin doses and more aggressive titration lead to lower HbA_{1c} levels, such a titration strategy is associated with an increased likelihood of AEs. Insulin therapy is commonly associated with hypoglycaemia and weight gain, whereas GLP-1 receptor agonists are associated with gastrointestinal side effects [1]. Nausea was among the most commonly reported AEs in all of the studies involving GLP-1 receptor agonists and, where reported, nausea was given as a common reason for withdrawal from the study [13], [14], [17], consistent with the overall safety profile of GLP-1 receptor agonists. Consistent with the AE profile for insulin and GLP-1 receptor agonists, the evidence from the current indirect comparison showed that treatment with GLP-1 receptor agonists was more likely to be associated with discontinuations due to AEs than NPH-insulin therapy. Although beyond the scope of this analysis, concern has previously been raised over a possible elevated risk of pancreatitis or pancreatic cancer associated with GLP-1 receptor agonists. However, a meta-analysis of 41 randomized clinical studies found no increase in the risk of pancreatitis associated with the use of GLP-1 receptor agonists [29], and recent incretin pancreatic safety reviews by both the US Food and Drug Administration (FDA) and the European Medicines Agency found no evidence of a causal relationship [30]. Similarly, thyroid C-cell hyperplasia and tumours associated with long-term liraglutide exposure in rodents led to concerns regarding a potential increased risk of medullary thyroid cancer with GLP-1 receptor agonists [31]. While an analysis of data from the FDA AE reporting system did seem to show an increased risk of pancreatic and thyroid cancer with incretin therapies, the data were inconsistent and have been discredited on the basis of a bias in reporting of events [32], [33]. Short-acting GLP-1 receptor agonists, such as lixisenatide and exenatide, have been associated with a small or non-significant effect on, or even a reduction in resting heart rate. However, several long-acting GLP-1 receptor agonists, including dulaglutide, liraglutide and exenatide once weekly, are associated with a significant increase in resting heart rate [34]. Currently it is not known whether these increases in heart rate could result in cardiovascular events; however, long-term, large-scale cardiovascular outcomes studies intended to confirm any cardiovascular risk associated with GLP-1 receptor agonists are currently underway.

Similar to the Methods Guide of the National Institute for Health and Care Excellence (NICE) in the UK, the method paper of the German Institute for Quality and Efficiency in Healthcare (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen; IQWiG) exhibits a strong preference for the use of direct comparisons from RCTs as a basis for establishing a benefit [35], [36]. If no direct head-to-head studies are available, both institutes men-

tion the possibility of applying methods for indirect comparisons. Evidence from indirect comparisons is not as robust as that from randomized head-to-head trials because of the potential for bias due to randomization not applying across different trials. However, adjusted indirect comparisons based on comparison of the magnitude of effect relative to the comparator in each of the two sets of controlled trials, rather than 'naïve' comparison of only the treatment arms of interest, can preserve some of the advantages associated with RCTs [37], [38]. In the context of this analysis, a number of limitations concerning the internal validity and generalizability of the studies included should be noted. Firstly, adjusted indirect comparisons using the method described by Bucher et al. [15] require a similarity of methodology, outcome measurement and of the included patient population, such that the relative effect estimates can be generalized across all trials using the same comparator. If conditions for both clinical similarity and methodological similarity between trials are not fulfilled, estimates arising from adjusted indirect comparisons may be both invalid and misleading. Even in the absence of evident differences, such as in this analysis, the strength of inference from indirect comparisons may be limited, and thus any conclusions made based on such data should be drawn with this in mind [38]. Secondly, there was a large difference in the population numbers of the RCTs included in this analysis. The small number of available studies focusing on once-daily NPH-insulin (basal-supported oral therapy) ($n=1$) or lixisenatide ($n=1$) was a possible limitation of this approach, which could have limited the statistical power of the indirect comparison. Some endpoints, such as hypoglycaemia and HbA_{1c} at target, had small data sets due to missing information from the original papers. However, this relates only to a limited proportion of patients and does not compromise the overall results. In addition, there was a high difference in the observed magnitude of hypoglycaemia rates between the different studies. Although there were small differences between studies in the original definition of hypoglycaemia, variations in definition did not appear to influence the frequency of hypoglycaemia. Fear of hypoglycaemic events could have influenced the number of self-reported events in patients knowingly receiving insulin. If randomization was effective, however, the potential for an overstated number of hypoglycaemic events would be assumed to be uniformly distributed between therapy arms, thus preventing a therapy-specific bias. However, uncertainty cannot be entirely ruled out owing to a lack of blinding with regards to insulin treatment. The possible bias is further reduced by comparing only effects versus a common reference with adjusted indirect comparisons.

Conclusions

The present adjusted indirect comparison analysis showed that lixisenatide was associated with a lower risk of hypoglycaemia and weight loss compared with NPH-

insulin at comparable glycaemic control as an add-on to metformin plus sulphonylurea in patients with T2DM. In contrast to NPH-insulin only, lixisenatide treatment was associated with weight loss. Therefore, lixisenatide is a beneficial treatment option for patients with T2DM with inadequate glycaemic control with OADs who, together with their physicians, are concerned about hypoglycaemia and weight gain.

Notes

Competing interests

Gerhard H. Scholz received lecture fees, honoraria and compensation for travel and accommodation costs for attending advisory boards from Abbott, Actavis, Astra-Zeneca, Bristol-Myers Squibb, Eli Lilly, Essex, Merck Sharp & Dohme, Novartis, Novo Nordisk, Solvay, Sanofi-Aventis and Takeda.

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Attachments

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- 000199_Attachment1.pdf (72 KB)
Appendix 1: Selection criteria used to assess studies for the oral antidiabetic drug and basal insulin systematic reviews
- 000199_Attachment2.pdf (98 KB)
Appendix 2: Flow diagram for study selection
- 000199_Attachment3.pdf (91 KB)
Appendix 3: Sensitivity analyses: indirect comparison of lixisenatide vs. NPH without consideration of the studies investigating exenatide or calculating the indirect comparison via insulin glargine as a reference
- 000199_Attachment4.pdf (342 KB)
Appendix 4: Single steps comparison summaries for HbA_{1C}, body weight and hypoglycaemic events

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